DATA EVALUATION RECORD

FLUTRIAFOL

Study Type: OPPTS 870.7485 [§85-1]; Metabolism Study in Rats

Work Assignment No. 5-1-151 S,T, and U; formerly 4-1-151 (MRIDs 47090412-47090414)

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DATA EVALUATION RECORD

STUDY TYPE: Metabolism in Rats; OPPTS 870.7485 (§85-1); OECD 417.

PC CODE: 128940 **DP BARCODE**: 340368

TEST MATERIAL (RADIOCHEMICAL PURITY): Flutriafol (>97%)

SYNONYMS: α-(2-fluorophenyl)-α-(4-fluorophenyl)-1*H*-1,2,4-triazole-1-ethanol; PP450

CITATION: Millais, A.J. (2004) [^{14}C]-Flutriafol metabolism in rats after single and repeated doses. Huntingdon Life Sciences Ltd., Huntingdon, Cambridgeshire, England. Laboratory Project No.: CHV 081/024050, August 16, 2004. MRID 47090414. Unpublished.

Jones, B.K. (1982) PP450 (Flutriafol): Excretion and tissue retention of a single oral dose (5 mg/kg) in the rat. Imperial Chemical Industries PLC, Macclesfield, Cheshire, UK. Laboratory Report No.: CTL/P/751, October 7, 1982. MRID 47090412. Unpublished.

Jones, B.K. (1986) Flutriafol: Biotransformation in the Rat. Imperial Chemical Industries PLC, Macclesfield, Cheshire, UK. Laboratory Study-Report No.: UR0149-CTL/P/856, June 12, 1986. MRID 47090413. Unpublished.

SUBMITTER/SPONSOR: Cheminova, Inc., 1600 Wilson Boulevard, Suite 700, Arlington, VA (originally sponsored by Imperial Chemical Industries PLC)

EXECUTIVE SUMMARY: In rat metabolism studies (MRIDs 47090412, 47090413, and 47090414), ^{14}C-flutriafol (>97% radiochemical purity) in polyethylene glycol 600 was administered to rats as a single oral gavage dose at 5 or 250 mg/kg body weight. Group sizes were 1 rat/sex in a preliminary study at 5 mg/kg, 2 rats/sex/dose in bile duct-cannulation studies, one group of 6 females at 250 mg/kg, and 4-5 rats/sex/dose in other dose groups. One group of 4 rats/sex received 14 consecutive daily doses at 5 mg/kg/day. ^{14}C-carbinol-flutriafol was administered to all groups, except one group of 2 rats/sex was treated with 5 mg/kg ^{14}C-triazole-flutriafol. Excreta (urine, feces, and bile [in some groups]) were collected, and analyzed for radioactivity concentration. Additionally, pools of selected excreta were analyzed to identify and quantify metabolites. Animals were sacrificed at 48 hours in the preliminary experiment and at 72 or 168 hours post-dose or post final dose in the other studies. Tissues were collected and analyzed for radioactivity concentration.

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More than 78% of the administered dose was recovered in the bile and urine of the single 5 mg/kg (both radiolabels) and 250 mg/kg dose groups. Absorption was generally similar between sexes, radiolabels, and between single and multiple dose regimes. Comparing absorption in 5 mg/kg groups to the 250 mg/kg groups, absorption remains extensive; however, a longer time is required for absorption to complete.

Total recoveries at 168 hours post-dose were 97-99% of the administered single dose and 115-125% daily dose in the multiple dose study. The administered dose was mostly eliminated within 48 hours at 5 mg/kg (86-97% of the single dose or 104% daily dose of the multiple dose groups) and at 250 mg/kg (68-85% dose, except bile duct-cannulated females which was 38% dose).

Only 0.04-0.05% of the dose was found in the expired carbon dioxide in a preliminary study. In the bile duct-cannulation study, most of the radioactivity was excreted in the bile (47-79% of the dose). In the single dose 5 mg/kg group (not bile duct-cannulated), similar amounts of radioactivity were excreted in the feces as in the urine, but only approximately half as much was excreted in the feces as in the urine at 250 mg/kg. Slightly more radioactivity was found in the urine of the multiple dosed animals compared to the single dosed animals. The excretion profile was generally similar between the sexes, and was also similar following 1, 5, 10, and 14 doses.

Tissue distribution was examined in animals sacrificed 168 hours post-dose. In the blood, radioactivity partitioned into the red blood cells. In animals receiving multiple daily 5 mg/kg doses, concentrations of radioactivity were higher in the blood cells than plasma of males (218-fold) and females (129-fold). Excluding blood cells and GI tract measurements, the highest concentrations were found in whole blood in males (190 ng equivalents flutriafol/g tissue in the single 5 mg/kg dose group, 8040 ng equiv/g in the 250 mg/kg dose group, and 1450 ng equiv/g in the multiple 5 mg/kg/day dose group) and in females (140 ng equivalents flutriafol/g tissue in the single 5 mg/kg dose group, 6740 ng equiv/g in the 250 mg/kg dose group, and 519 ng equiv/g in the multiple 5 mg/kg/day dose group). In both sexes and all groups, concentrations of radioactivity were relatively high in both liver and kidneys. Other organs with high concentrations in one or more groups included the adrenal glands, spleen, and pituitary. The distribution profiles were generally similar between species, dose level, and single vs multiple dose regime. A 50-fold increase in dose resulted in an approximately 42-48-fold increase in radioactivity concentrations in the whole blood; thus, the concentrations were roughly proportional to the dose.

The total amount of radioactivity isolated in the tissues and carcass was miniscule: <1% of the administered dose (single dose groups) or 3% of the daily administered dose (multiple dose group). Also, the amount of the dose remaining in the body (GI tract and contents, tissues, and remaining carcass) after 168 hours was <1.1% of the administered dose regardless of sex, radiolabel position, or dose. For these reasons, bioaccumulation in all dose groups was considered unlikely.

The parent was isolated in only trace amounts in the urine and feces (<0.5% of the administered dose) and more than 19 metabolites were isolated, indicating extensive metabolism of flutriafol.

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In general, metabolism profiles were similar between sexes. The metabolism profile in urine was similar between the 250 mg/kg dose group and the multiple 5 mg/kg dose group, but the metabolism profiles in feces resulted in the isolation of greater amounts of identified compounds in the high dose group. Summarizing the Sponsor's stated results in MRID 47090413 (data not provided); the metabolic profiles were similar regardless of the matrix (feces, urine, or bile), the dose, the sex, or the radiolabel.

The primary site for metabolism was the 2-fluorophenyl ring. The initial metabolic step was probably epoxidation followed by either rearrangement to form the dihydrodiol isomers or to form hydroxy or dihydroxy metabolites. The hydroxyl groups on these primary metabolites may then be either conjugated with glucuronic acid or methylated. A second, minor route for metabolism of flutriafol was via the removal of the triazole ring to form 1-(2 fluorophenyl)-1-(4-fluorophenyl)-ethandiol, which is then conjugated with glucuronic acid.

This metabolism study in the rat is classified **acceptable/guideline** and satisfies the guideline requirement for a metabolism study [OPPTS 870.7485, OECD 417] in rats.

COMPLIANCE: Signed and dated GLP Compliance, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test compound

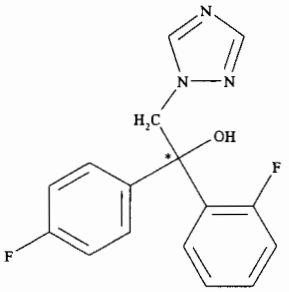
Radiolabeled test material: ^{14}C-carbinol-labelled flutriafol

Radiochemical purity: >97%

Specific activity: 1.835 GBq/mmol (Rad 164) or 2.17 GBq/mmol (Y01433/012/001 and Y01433/012/002)

Batch no. or CTL reference no.: Rad 164, Y01433/012/001 or Y01433/012/002 (2 different batches)

Structure



* = position of ^{14}C label

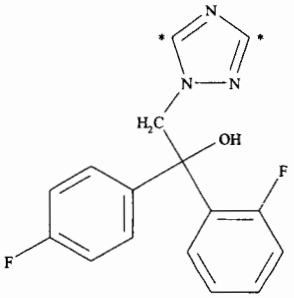
Radiolabeled test material: ^{14}C-triazole-labelled flutriafol

Radiochemical purity: >98%

Specific activity: 2.22 GBq/mmol

CTL reference no.: Y01433/004/001

Structure



* = position of ^{14}C label

Non-radiolabeled test material: Flutriafol

Description: White crystalline solid

Lot no. or CTL reference no.: ASJ-10005-01 or Y01433/003/003

Purity: 99% (ASJ-10005-01) or 94% (Y01433/003/003)

Contaminants: Not reported

CAS # of TGAI: 76674-21-0

2. Vehicle and/or positive control: Polyethylene glycol 600

3. **Test animals:**

Species:	Rat	
Strain:	Sprague Dawley (Crl:CD® (SD) IGS BR for MRID 47090414; Alpk:AP (for MRID 47090413) or Alderley Park strain, Wister-derived, albino (for MRID 47090412)	
Age/ weight at study initiation:	6-10 weeks; weight of rats (both sexes): 176-274 g	
Source:	Charles River UK Ltd., Margate, Kent, UK or Animal Breeding Unit, Alderley Park, Macclesfield, Cheshire, UK	
Housing:	Individually in metabolism cages (Forth Tech Ltd., Dalkeith, Scotland), glass metabolism cages (Jencons Ltd., Hemel Hempstead, UK), restraining cages (for biliary duct-cannulated rats), or housed by sex in battery cages, as appropriate	
Diet:	VRF1C standard laboratory diet (Using d'Alimentation Rationnele, Special Diet Services Ltd., Essex, UK) or PCD rat diet (Special Diet Services Ltd., Essex, UK) , *ad libitum*	
Water:	Tap water, *ad libitum*	
Environmental conditions:	**Temperature:**	21±2°C
	Humidity:	27-70%
	Air changes:	25/hour
	Photoperiod:	12-hour light/12-hour dark
Acclimation period:	4-10 days	

4. **Preparation of dosing solutions:** Unlabelled flutriafol and [^{14}C]-radiolabelled flutriafol were mixed together with acetonitrile or ethanol in a conical flask to achieve the desired specific activity and enough material for all dose preparations. The solvent was removed by nitrogen convection followed by vacuum desiccation. Dose formulations were prepared by dissolving a weighed amount of flutriafol in polyethylene glycol 600 (2 mg/mL for low dose and 100 mg/mL for high dose) using sonication, mixing, and warming. Samples were taken for purity and stability analyses. Stability was assessed up to 120 hours after preparation at 4°C.

B. STUDY DESIGN AND METHODS

1. **Group arrangements:** Animals were assigned to the test groups noted in Table 1. Further information regarding randomization and dose-selection rationale was not provided. In the bile duct cannulation study, animals were anesthetized with halothane BP, and their bile ducts were exposed. The bile ducts were ligated above the duodenum, and a cannula was inserted and attached.

TABLE 1: Dosing groups for pharmacokinetic studies of Flutriafol [a]

Dose Group	Nominal dose (mg/kg)	[^{14}C]-Label[b]	Actual average dose or range (mg/kg) in both sexes	# Rats/dose group	Comments
Preliminary study: Single oral low dose	5	C	5.19	1/sex	In MRID 47090412, urine, feces, cage wash, and expired carbon dioxide were collected for up to 48 hours, after which the animals were sacrificed, and whole-body autoradiography was performed.
Single oral low dose	5	C	4.98	5/sex	In MRID 47090412, urine, feces, and cage wash samples were collected for up to 168 hours after dosing, and radioactivity was quantified in the samples. The animals were then killed, and tissue concentrations of radioactivity were measured.
Single oral high dose	250	C	243-246	4/sex	In MRID 47090414, urine, feces, and cage wash samples were collected for up to 168 hours after the final (or single) dose, and radioactivity was quantified in the samples. Tissue concentrations of radioactivity were measured at 168 hours after the final (or single) dose. Metabolites in the excreta were isolated and identified when possible.
Multiple low dose	5 mg/kg for 14 consecutive days	C	4.86-5.09		
Single oral high dose	250	C	236	6 females	In MRID 47090413, urine and feces were collected for up to 72 hours post-dose, and radioactivity was quantified in the samples. Metabolites in the urine and feces were isolated and identified when possible.
Single oral high dose (bile duct-cannulated rats)	250	C	250	2/sex	In MRID 47090413, bile and urine were collected for up to 72 hours post-dose, and radioactivity was quantified in the samples. Metabolites in the bile and urine were isolated and identified when possible.
Single oral low dose (bile duct-cannulated rats)	5	C	5.04	2/sex	In MRID 47090413, bile, urine, and feces were collected for up to 72 hours post-dose, and radioactivity was quantified in the samples. Metabolites in the bile, urine, and feces were isolated and identified when possible.
		T	4.95		

a The order of presentation in this table presents the preliminary study first (MRID 47090412), information necessary in a Tier 1 study (MRIDs 47090412 and 47090414) next, and finally information that may be required in a Tier 2 study (MRID 47090413).

b ^{14}C-carbinol-flutriafol (designated C) and ^{14}C-triazole-flutriafol (designated T) were used in these studies.

2. **Dosing and sample collection:** ^{14}C-carbinol-flutriafol dosing solutions were administered by a single oral gavage dose at 5 or 250 mg/kg or for 14 consecutive daily doses at 5 mg/kg. Additionally, a ^{14}C-triazole-flutriafol dosing solution was administered by a single gavage dose at 5 mg/kg. The formulations were administered in a volume of 2.5 mL/kg bw (MRID 47090414) or 5 mL/kg bw (MRIDs 47090412 and 47090413) within 2 hours of preparation. The specific activities of the dosing solutions in MRID 47090412 were 1.90 MBq/mg for the whole-body autoradiography study and 373 kBq/mg for the other study. The average specific activity administered was not reported in MRID 47090414, but individual data (dpm

and mg) were reported in Appendix 3, pages 91-95. In MRID 47090413, the average specific activity administered was 10.35-10.43 kB/mg for the low dose and 429-536 kB/mg in the high dose. The animals were not fasted. Actual dosages were determined gravimetrically.

a. Pharmacokinetic studies

1. **Collection:** All excreta were collected separately from each animal into separate receivers cooled with solid CO_2. In the preliminary study detailed in MRID 47090412, expired air was drawn sequentially through a pair of columns containing 2 N aqueous sodium hydroxide. ^{14}C-labelled carbon dioxide was absorbed in these columns and measured at 24 and 48 hours after dosing. Urine and feces were also collected at 24 and 48 hours. The cages were washed with methanol:water (1:1) at 48 hours, and the cage wash was collected. The rats were killed by Fluothane anesthesia at 48 hours after dosing. The animals were immediately frozen in a hexane-solid carbon dioxide slurry (-70°C), and embedded separately into 2% carboxymethyl cellulose to form solid blocks. The 2 frozen blocks were transferred to a cryostat at -20°C and longitudinal sagital sections (20 µm thickness) were cut mechanically using a microtome. Sections displaying organs of interest were mounted on adhesive tape and freeze-dried at -20°C for 48 hours. Whole-body autoradiography was performed by contact of the freeze-dried sections with X-ray film for 1 or 2 months in a light-tight box.

   In the main study detailed in MRID 47090412, urine and feces were collected at 24 hour intervals for 7 days. Cages were washed with methanol:water (1:1) following the removal of the animals from the metabolism cages, and the washes were collected. Following sacrifice at 7 days post-dose by Fluothane anesthesia, a blood sample from each animal was collected by cardiac puncture. The residual carcasses were kept after the following tissues/organs were excised, weighed, and collected for analysis:

adrenal glands	lungs	ovaries (with fallopian tubes)/testes
brain	kidneys	pituitary gland
fat	liver	spleen

   In MRID 47090414, urine and feces were collected during 0-6 and 6-24 hours and during subsequent 24 hour intervals following the single dose treatments. In the multiple dose treatments, urine and feces were collected during 0-6 and 6-24 hours after doses 1, 5, 10, and 14, and during subsequent 24 hour periods up to 168 hours after dose 14 (final dose). The cages were washed with water at 24 hours after dose 1, 5, 10, and 14, and after subsequent 24 hour periods up to 168 hours after dose 14. The urine, feces, and washings were retained for measurement of radioactivity. Immediately prior to sacrifice (168 hours after the final dose) and under isoflurane anesthesia, a blood sample from each animal was collected by cardiac puncture. A portion of each blood sample was retained, while the remaining blood was centrifuged to obtain plasma. The animals were sacrificed by cervical dislocation, and the same

tissues/organs were excised and weighed as in MRID 47090412. Additionally, the GI tract (with contents), heart, and muscle were collected.

In MRID 47090413, urine and feces were collected at daily intervals for 3 days, except fecal samples were not collected from the 250 mg/kg bile duct-cannulated rats. Bile was also collected from each bile duct-cannulated rat in 24-hour intervals for 3 days. The weights of each daily sample of urine and bile were determined.

2. **Storage:** Whole blood was stored at approximately 4°C, all other samples were stored at approximately -20°C.

3. **Preparation:** In MRID 47090412, aliquots of whole blood samples dry powdered fecal residues were combusted. Additional aliquots of whole blood samples were centrifuged to obtain plasma. Samples of plasma, urine, cage wash, fecal extracts, and the 2 N sodium hydroxide used to trap ^{14}C-carbon dioxide were radioassayed. Fat, testes, kidneys, liver, lung, brain, and fallopian tubes were homogenized in water and combusted, while ovaries, adrenals, and pituitary glands were combusted. The residual carcasses were homogenized in chloroform : methanol (2:1); homogenates were filtered; and the residues rinsed with solvent washings from the homogenizer. The filtrates were radioassayed, and the residues were air-dried, ground to a fine powder, and combusted.

   In MRID 47090414, weighed aliquots of urine and cage wash samples were radioassayed. Fecal samples were sequentially homogenized with extraction solvent (acetonitrile, acetonitrile, and acetonitrile : water [1:1, v/v]). Aliquots of supernatant were weighed and radioassayed. The fecal residues were allowed to air-dry, and were weighed, homogenized, and combusted. Tissue/organ samples were weighed and combusted. For the low level repeat oral dose animals, adrenal glands, pituitary glands, and ovaries were combusted *in toto*. For the high level dose, adrenal glands, pituitary glands, and ovaries were solubilized in NCS II tissue solubilizer at approximately 55°C for *ca* 24 hours before being taken *in toto* for radioassay. Liver (high dose phase), brain, fat, heart, kidneys, lungs, muscle, spleen, and testes were macerated with scissors, while liver samples from the low dose phase were homogenized and combusted. The residual carcasses were individually solubilized using a digestion medium of 2 M sodium hydroxide solution containing water, methanol, and Triton X-405 (6/3/1, v/v/v) for 48 hours at 55°C. Weighed aliquots were radioassayed.

   In MRID 47090413, aliquots of the urine and bile samples were radioassayed. Daily fecal samples from the bile duct-cannulated rats were homogenized in 0.5% aqueous solution of carboxymethyl cellulose and oxidized. Fecal samples from rats not cannulated were homogenized in methanol, and supernatants were radioassayed. Solvent extracted fecal residues were air-dried, weighed, ground to a fine powder, and combusted.

4. **Analysis:** Compensation was made for the efficiency of oxidation of test samples relative to [^{14}C]-standard oxidation efficiency. Radiation was quantified by mixing prepared replicate samples (sometimes diluted) with scintillation fluid followed by liquid scintillation counting (LSC) with automatic quench correction. Background activity and counting efficiency was corrected by using an external source. Radioactivity in gross amounts of less than twice background was considered to be below the limit of accurate detection.

b. **Metabolite characterization studies:** In MRID 47090414 in the multiple dose study, urine pools were prepared separately by sex by combining equal proportions of the total weight of urine collected between 0-6 and 6-24 hours after doses 1, 5, 10, and 14. Pooled urine samples were analyzed directly. Fecal extract pools were prepared separately by sex by combining equal proportions of the total weight of fecal extracts (1-3) of the 6-24 hour samples after doses 1, 5, 10, and 14. For 3 of the animals, it was necessary to include an equal proportion of the 0-6 hours fecal extract 1 to ensure each pool contained >90% of the extracted radioactivity during a 24 hour period. A subsample of each pooled fecal extract was concentrated by nitrogen convection, reconstituted in a small volume of the initial HPLC mobile phase (generally 0.1% aqueous trifluoroacetic acid : acetonitrile, 4:1, v/v), and analyzed.

In MRID 47090414 in the 250 mg/kg treated group, urine pools were prepared separately by sex by combining equal proportions of the total weight of urine collected between 24 and 96 hours after dosing. Pooled urine samples were analyzed directly. Fecal extract pools were prepared separately by sex by combining equal proportions of the total weight of fecal extracts (1-3) of the 6-96 hour samples. A subsample of each pool was concentrated by nitrogen convection, and reconstituted in 0.1% aqueous trifluoroacetic acid : acetonitrile, 4:1. Solid debris was removed by centrifugation prior to chromatographic analysis.

In MRID 47090414, aliquots of each urine pool were separately mixed with equal volumes of 0.2 M sodium acetate buffer containing a mixture of enzymes (β-glucuronidase/sulphatase, Type H1 from *Helix pomatia*) and incubated at 37°C for approximately 24 hours. Glucuronidase and sulphatase activities were confirmed. Enzyme-treated, inhibited, and control urine samples were analyzed directly.

In MRID 47090413 in the 250 mg/kg females (not cannulated), the total 0-72 h urine was pooled, and a sample was removed for TLC. The remaining urine was freeze-dried, and the residue extracted with methanol for analysis. Aliquots of 5% of each daily fecal extract sample collected over 0-72 h was pooled, concentrated by rotary film evaporation, and analyzed. Unextracted fecal residues were not analyzed.

In MRID 47090413 in the bile duct-cannulated animals, weights of urine representing similar proportions of each daily sample (0-72 h) were pooled for each pair of similarly dosed rats. Each pool was evaporated to dryness; residues were extracted with methanol; and the extracts were analyzed. Urinary fraction (designated M1) was evaporated to dryness and redissolved in distilled water. Solutions were adjusted to pH 5.0 prior to the

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addition of β-glucuronidase (Type B from bovine liver) or pH 7.0 prior to the addition of sulphatase (type V from limpets). Enzyme preparations were incubated at 37°C for up to 72 hours. Samples were adjusted to pH 7.0 and extracted with diethyl ether. A minor portion of the ether extract was removed and the content derivatized with diazomethane, while the majority was concentrated and analyzed. Derivitization occurred at ambient temperature for 30 minutes. Excess diazomethane was evaporated under a stream of nitrogen, and the samples were analyzed by gas liquid chromatography. Fecal samples were not analyzed due to their low radioactivity content. In the 250 mg/kg rats, weights of bile representing 80% of each daily sample were pooled by sex. A sample of each total pool was removed for comparative TLC. The residual pools were freeze-dried; the residues were extracted with methanol; and the extracts were analyzed. Aliquots of these bile sample extracts were hydrolyzed with hydrochloric acid to adjust pH values over a range of 9.0 to less than 1.0. Preparations were heated at temperatures of 80-100°C for between 30 minutes and 17 hours. Additional aliquots of the bile samples were evaporated to dryness and redissolved in distilled water, and subjected to enzyme hydrolysis as above. Weights of bile samples from rats treated at 5 mg/kg representing 5% of each daily sample collected over 72 hours after dosing were pooled for each pair of similarly dosed animals. Pools were rotary-evaporated to dryness; residues were extracted with methanol; and the extracts were analyzed.

Quantitation of metabolites in MRIDs 479090414 and 47090413 was performed using an HPLC with a radiometric detector. Normal phase TLC was used for analysis of urine and fecal extracts including co-chromatography, and the purification of metabolites for analysis by nuclear magnetic resonance spectroscopy. Metabolite identification was also accomplished by GC-MS, LC-MS, LC-MS/MS, and NMR.

3. **Statistics:** Only descriptive statistics (means and standard deviations) were reported.

II. RESULTS

A. **PRELIMINARY STUDY:** At 48 hours after dosing, total radioactivity recovered was 90% in the male and 99% in the female. Only 0.04-0.05% of the dose was present in the expired carbon dioxide; consequently, carbon dioxide was not collected in later studies. Most of the radioactivity was excreted within the first 24 hours, by which time a total of 73-85% of the dose was isolated in the excreta of each sex. By 48 hours after dosing, 88-97% of the dose was found in the excreta of each sex, and 1-2% of the dose was isolated in the cage wash. As only 1 animal/sex was tested in this preliminary study, comparisons of radioactivity levels by sex or quantity found in feces vs urine are discussed in the main studies. At 48 hours post-dose, autoradiography showed that the bulk of the radioactivity was present in the contents of the alimentary tract between the stomach and the rectum. Lesser amounts of radioactivity were present in the liver. Distribution in the liver was homogeneous in the females, but displayed a reticular appearance in the males. This appearance suggested that the radiolabelled material was concentrating preferentially to a particular area of the lobule in males. Radiation was found in the corticomedullary junction of the kidneys in both sexes.

Traces of radioactivity were present in the adrenals of females. Levels of radioactivity in other tissues/organs of either sex were considered insignificant.

B. PHARMACOKINETIC STUDIES

1. **Absorption/Elimination:** More than 78% of the administered dose was recovered in the bile and urine of the single 5 mg/kg (both radiolabels) and 250 mg/kg dose groups (Table 2a). The rapidity of absorption is unknown as pharmacokinetic parameters were not determined. There were only 2 rats/group in the bile duct-cannulated groups; however, absorption was generally similar between sexes and radiolabels. The bile duct-cannulation study demonstrated that most of the radioactivity found in the feces was absorbed and excreted via the bile. Absorption was similar between groups receiving a single 5 mg/kg dose and groups that received multiple 5 mg/kg doses (Table 2b). Comparing absorption in the 5 mg/kg groups to the 250 mg/kg groups, absorption remains extensive; however, a longer time is required for absorption to complete.

   Total recoveries at 168 hours post-dose were 97-99% of the administered single dose and 115-125% of the daily dose in the multiple dose study. The administered dose was mostly eliminated within 48 hours at 5 mg/kg (86-97% of the single dose or 104% daily dose of the multiple dose groups) and at 250 mg/kg (68-85% dose, except bile duct-cannulated females which was 38% dose).

   Most of the radioactivity was excreted in the bile (47-79% of the dose). The Sponsor estimated that approximately half of this biliary radioactivity was excreted directly in the feces, and the remainder was reabsorbed for subsequent elimination, mainly in the urine.

   In the single dose 5 mg/kg group (not bile duct-cannulated), similar amounts of radioactivity were excreted in the feces as in the urine, but only approximately half as much was excreted in the feces as in the urine at 250 mg/kg (Table 2b). Slightly more radioactivity was found in the urine of the multiple dosed animals compared to the single dosed animals. The excretion profile was generally similar between the sexes, and was also similar following 1, 5, 10, and 14 doses (Table 2c). Results from the 6 females treated at 250 mg/kg (MRID 47090413; data not shown) demonstrated a similar excretion profile to the 250 mg/kg females (MRID 47090414; Table 2b).

TABLE 2a. Recovery of radioactivity in tissues and excreta of rats after administration of ^{14}C-flutriafol [a]

Matrix	Percent of radioactive dose recovered					
	Single 5 mg/kg dose [b]		Single 250 mg/kg dose [b]		Single 5 mg/kg dose [c]	
	Male	Female	Male	Female	Male	Female
Urine (0-24 h)	7.1±0.4	11.1±5.0	4.2±0.7	6.1±0.2	9.1±0.5	14.0±5.1
Urine (24-48 h)	4.3±3.6	13.7±6.1	13.0±3.8	11.1±3.5	11.2±2.0	9.7±1.6
Feces (0-24 h)	0.1±0.0	0.2±0.3	ND	ND	1.3±1.7	0.2±0.1
Feces (24-48 h)	0.4±0.1	2.3±2.3	ND	ND	4.7±0.4	0.4±0.0
Bile (0-24 h)	63.9±20.2	45.4±7.6	23.8±3.0	6.1±2.5	42.6±3.5	56.8±3.2
Bile (24-48 h)	15.2±17.4	12.8±1.9	44.2±2.0	14.6±4.0	19.6±5.8	16.0±0.1
Urine (0-72 h)	11.9±2.8	25.0±1.4	18.8±3.7	31.4±3.6	22.0±1.9	24.1±3.7
Feces (0-72 h)	0.8±0.1	3.9±3.8	ND	ND	10.4±0.1	1.8±1.0
Bile (0-72 h)	79.3±2.7	58.3±9.4	71.0±1.5	46.9±3.9	62.7±2.4	73.0±3.2
Total excreted (0-72 h)	92.0±0.2	87.2±4.3	89.7±2.2	78.2±0.3	95.1±0.6	98.9±1.4

a Data (n=2; mean ± SD) were obtained from Tables 2-4 on pages 32-34 of MRID 47090413. Values were calculated by the reviewers from the cited data. Note that while there were only 2 animals/group, mean ± SD is reported in this table for consistency of data presentation throughout this DER.
b ^{14}C-carbinol-flutriafol was administered.
c 14C-triazole-flutriafol was administered
ND Not determined

TABLE 2b. Recovery of radioactivity in tissues and excreta of rats after administration of ^{14}C-carbinol flutriafol [a]

Matrix	Percent of radioactive dose recovered					
	Single 5 mg/kg dose		Single 250 mg/kg dose		Multiple 5 mg/kg dose [b]	
	Male	Female	Male	Female	Male	Female
Urine (0-24 h) [c]	37.8±4.5	47.5±4.1	19.7	22.1	48.6	60.6
Urine (24-48 h)	5.7±1.4	3.3±1.1	29.8±1.7	34.1±3.3	9.7±2.1	4.6±1.2
Feces (0-24 h)	33.4±5.8	37.5±7.5	4.0	4.4	31.5	32.6
Feces (24-48 h)	14.6±4.9	6.9±3.8	14.1±0.8	12.6±3.4	14.1±3.1	6.1±2.9
Urine (0-168 h)	45.4±4.6	51.7±4.8	60.6±3.6	67.5±4.4	64.2±9.3	68.2±4.9
Feces (0-168 h)	50.8±5.3	45.2±5.0	33.1±3.1	26.9±4.3	54.7±11.5	40.8±1.6
Cage wash (0-168 h)	0.6±0.1	0.6±0.4	2.8±0.4	4.3±2.0	3.4±1.3	2.9±1.0
Total excreted (0-168 h) [d]	96.8	97.6	96.6	98.8	122.2	112.0
Tissues + carcass	0.7±0.1	0.4±0.1	0.2±0.0	0.2±0.0	3.0±0.4	3.0±0.6
Total recovered (0-168 h)	97.5±1.0	98.0±0.4	96.8±1.6	99.0±0.7	125.2±4.2	115.0±2.0

a Data (n=4-5; mean ± SD) were obtained from Tables 1-8 on pages 22-33 of MRID 47090412 and Tables 1-3 on pages 36-39 of MRID 47090414.
b 14 consecutive daily doses were administered, and results after the final dose are reported as % daily dose.
c Data for the 250 mg/kg and repeated 5 mg/kg dose groups were calculated by the reviewers as the sum of the values for 0-6 and 6-24 h.
d Data were calculated by the reviewers as total recovered – (tissues + carcass).

TABLE 2c. Recovery of radioactivity in tissues and excreta of rats after up to 14 consecutive daily doses of ^{14}C-carbinol flutriafol [a]

Sex and matrix		Dose # (results in percent daily dose recovered)			
		1	5	10	14 [b]
Male	Urine	50.2±6.4	49.8±5.2	50.8±4.7	64.2±9.3
	Feces	29.4±6.4	36.4±10.6	31.4±11.5	54.7±11.5
	Cage wash	2.0±0.4	1.7±0.5	2.7±1.1	3.41±1.3
	Total	81.6±1.3	88.0±7.3	84.9±7.9	125.2±4.2
Female	Urine	53.9±1.0	54.9±3.9	57.1±5.1	68.2±4.9
	Feces	33.1±2.2	36.7±4.8	39.8±5.1	40.8±1.6
	Cage wash	2.2±1.4	2.1±0.6	2.2±0.9	2.9±1.0
	Total	89.3±1.3	93.7±6.4	99.2±2.6	115.0±2.0

a Data (n=4; mean ± SD) were obtained from Tables 1 on pages 36-37 of MRID 47090414.

b After the final dose, collections were made up to 168 hours post-dose, whereas collections were only made up to 24 hours after doses 1, 5, and 10. Also, the total radioactivity recovered after the final dose includes the 3.0% daily dose recovered in the carcass of each sex.

2. **Tissue distribution:** Tissue distribution was examined in animals sacrificed 168 hours post-dose. In blood, radioactivity partitioned into the red blood cells. In animals receiving multiple doses, concentrations of radioactivity were higher in the blood cells than plasma of males (218-fold) and females (129-fold; Table 3). Excluding blood cells and GI tract measurements, the highest concentrations in males were found in whole blood (190 ng equivalents flutriafol/g tissue in the single 5 mg/kg dose group, 8040 ng equiv/g in the 250 mg/kg dose group, and 1450 ng equiv/g in the multiple 5 mg/kg/day dose group), and high concentrations were also found in the liver (30 ng equiv/g in the single 5 mg/kg dose group, 1820 ng equiv/g in the 250 mg/kg dose group, and 724 ng equiv/g in the multiple 5 mg/kg/day dose group). Excluding blood cells and GI tract measurements, the highest concentrations in females were found in whole blood (140 ng equivalents flutriafol/g tissue in the single 5 mg/kg dose group, 6740 ng equiv/g in the 250 mg/kg dose group, and 519 ng equiv/g in the multiple 5 mg/kg/day dose group), and high concentrations were also found in the kidney (20 ng equiv/g in the single 5 mg/kg dose group, 2210 ng equiv/g in the 250 mg/kg dose group, and 861 ng equiv/g in the multiple 5 mg/kg/day dose group). In both sexes and all groups, concentrations of radioactivity were relatively high in both liver and kidneys. Other organs with high concentrations included the adrenal glands in the single 5 mg/kg females (40 ng equiv/g) and 250 mg/kg/day females (3200 ng equiv/g); spleen in the 250 mg/kg males (1640 ng equiv/g) and the multiple 5 mg/kg/day males and females (579-673 ng equiv/g); and pituitary in the multiple 5 mg/kg/day males (521 ng equiv/g). Thus, the distribution profiles were generally similar between species, dose level, and single vs multiple dose regime. A 50-fold increase in dose resulted in an approximately 42-48-fold increase in radioactivity concentrations in the whole blood; thus, the concentrations were roughly proportional to the dose.

Comparison of radioactivity concentrations in tissues from the multiple dose study with the single dose study suggests that bioaccumulation occurs; however, the analyses performed in 1982 (MRID 47090412) of the single 5 mg/kg dosed animals were not the same as those performed in 2004 (MRID 47090414) for the multiple 5 mg/kg dosed animals; consequently, a direct comparison could not be performed. Again, pharmacokinetic parameters were not determined; also, analysis of tissues at different time points was not

conducted. These analyses could have helped answer the question of bioaccumulation. The total amount of radioactivity isolated in the tissues and carcass was miniscule: <1% of the administered dose was isolated in the single 5 mg/kg dose groups and 250 mg/kg dose groups and only 3% of the daily administered dose was isolated in the multiple 5 mg/kg dose group. Also, the amount of the dose remaining in the body (GI tract and contents, tissues, and remaining carcass) after 168 hours was <1.1% of the administered dose regardless of sex, radiolabel position, or dose. For these reasons, bioaccumulation in all dose groups was considered unlikely.

TABLE 3. Distribution of radioactivity in rat tissues/organs 168 hours after administration of ^{14}C-carbinol flutriafol [a]

Organ/tissue	ng equivalents flutriafol/g tissue					
	Single 5 mg/kg dose		Single 250 mg/kg dose		Multiple 5 mg/kg dose [b]	
	Male	Female	Male	Female	Male	Female
Blood cells	NR	NR	NR	NR	3490±1090	1290±440
Whole blood	190±30	140±40	8040±1120	6740±1130	1450±468	519±184
Plasma	<10	10±0	89±16	86±12	16±3	10±1
Liver	30±0	20±0	1820±332	1200±159	724±167	310±13
Kidneys	20±0	20±0	1540±99	2210±409	447±61	861±56
Residual carcass	60±10	40±10	NR	NR	NR	NR

a Data (n=4-5; mean ± SD) were obtained from Tables 3(a) on page 24 and Table 7(a) on page 30 of MRID 47090412 and Tables 5-6 on pages 41-42 of MRID 47090414.

b 14 consecutive daily doses were administered, and results after the final dose are reported.

NR Not reported

B. METABOLITE CHARACTERIZATION STUDIES: GC-MS, LC-MS, LC-MS/MS, and NMR analyses combined with enzyme and acid hydrolysis studies revealed the presence of more than 19 radioactive compounds in the urine and feces and allowed the identification of some of these compounds (Table 4). Total radiation accounted for in the identified and unidentified components was 87-94% dose at 250 mg/kg and 60-76% at 5 mg/kg (multiple dose); total identified amounted to 69-72% dose at 250 mg/kg and 40-55% dose at 5 mg/kg (multiple dose). The proposed metabolic pathway is presented as Figure 24 on page 84 of MRID 47090414 and is included as an Attachment to this DER.

At least thirteen additional metabolites were isolated but not identified. The parent and the following metabolites were identified:

M3 1-(2-fluoro-4,5-(*cis*)-dihydroxy-cyclohexa-2,6-diene)-1-(4-fluorophenyl)-2-(1,2,4triazol-1-yl) ethanol (major)
1-(2-fluorophenyl)-1-(4-flurophenyl-ethan-1,2-diol glucuronide (minor)

M5 1-(2-fluoro-4,5-(*trans*)-dihydroxy-cyclohexa-2,6-diene)-1-(4-flurophenyl)-2-(1,2,4triazol-1-yl) ethanol

M6 1-(2-fluoro-4,5-(*trans*)-dihydroxy-cyclohexa-2,6-diene)-1-(4-flurophenyl)-2-(1,2,4triazol-1-yl) ethanol

M8 1-(2-fluoro-4-hydroxyphenyl)-1-(4-fluorophenyl)-2-(1,2,4triazol-1-yl) ethanol glucuronide and
1-(2-fluoro-4-hydroxy-5-methoxyphenyl)-1-(4-fluorophenyl)-2-(1,2,4triazol-1-yl) ethanol glucuronide

M15 1-(2-fluoro-4-hydroxy-5-methoxyphenyl)-1-(4-fluorophenyl)-2-(1,2,4triazol-1-yl) ethanol NB the order of 4,5 substitution is not confirmed for this compound, AND
1-(2-fluoro-4-hydroxyphenyl)-1-(4-fluorophenyl)-2-(1,2,4triazol-1-yl) ethanol

M18 1-(2-fluorophenyl)-1-(4-fluorophenyl) ethan-1,2-diol

The parent was isolated in only trace amounts in the urine and feces (<0.1% of the administered dose, except 0.2-0.4% dose in the feces of the multiple 5 mg/kg dose group). In the single 250 mg/kg dose group, metabolites representing ≥5% of the administered dose included the following: (i) M5, M6, M3, and M15 in the urine of both sexes; (ii) M8 in the urine of females; (iii) M6, M3, and M15 in both sexes in the feces; and (iv) M18 in the feces of males. In the multiple 5 mg/kg dose group, metabolites representing ≥5% of the administered dose included the following: M8, M5, M6, and M3 in the urine of both sexes; and M6 in the feces of females. Unknowns representing more than 5% dose included M9 in the urine of the multiple 5 mg/kg dose males and M16 in the feces of the 250 mg/kg dose males and females. Together, these data indicate that flutriafol is extensively metabolized.

In general, metabolism profiles were similar between sexes. The metabolism profile in urine was similar between the 250 mg/kg dose group and the multiple 5 mg/kg dose group, but the metabolism profiles in feces resulted in the isolation of greater amounts of identified compounds in the high dose group.

Results from MRID 47090413 were not tabulated. Summarizing the Sponsor, the metabolic profiles were similar regardless of the matrix (feces, urea, or bile), the dose, the sex, or the radiolabel. Comparative studies with ^{14}C-carbinol- and ^{14}C-triazole-labeled flutriafol indicated that only a minor amount of cleavage of the triazole moiety occurred. Urinary metabolites included M15 (11% of administered dose), M8 (8% dose), M5 and M6 (8-10% dose, each), and probably M3 (8% dose). The compound designated as M2C was assigned a structure that differs from M3; however, the structures are similar enough that the compounds could be the same, and M3 is more likely the correct structure.

The primary site for metabolism was the 2-fluorophenyl ring. The initial metabolic step was probably epoxidation followed by either rearrangement to form the dihydrodiol isomers or to form hydroxy or dihydroxy metabolites. The hydroxyl groups on these primary metabolites may then be either conjugated with glucuronic acid or methylated. A second, minor route for metabolism of flutriafol was via the removal of the triazole ring to form 1-(2 fluorophenyl)-1-(4-fluorophenyl)-ethandiol, which is then conjugated with glucuronic acid.

TABLE 4. Metabolite profile of excreta collected from rats after treatment with ^{14}C-carbinol flutriafol [a]

Dose	Percent of administered dose			
	Single 250 mg/kg dose		Multiple 5 mg/kg dose [b]	
Compound	Male	Female	Male	Female
Urine				
Parent	<0.1	<0.1	<0.1	<0.1
M8	4.6	8.6	7.6	12.7
M5	6.4	7.5	6.8	11.9
M6	6.6	9.0	6.5	9.9
M3	6.6	8.7	5.0 [c]	7.8
M15	15.2	6.6	4.5	1.3
M18	2.5	1.6	0.4	<0.1
Feces				
Parent	<0.1	<0.1	0.4	0.2
M6	8.6	15.9	3.8	5.7
M3	5.0	6.3	2.5	2.4
M15	5.9	5.9	1.1	1.8
M18	7.8	2.4	0.9	0.3
M5	<0.1	<0.1	0.8	1.2
M8	<0.1	<0.1	<0.1	<0.1
Total identified [d]	69.2	72.5	40.3	55.2
Urine				
Unknown M9	<0.1	<0.1	6.4	4.9
Unknown M11	1.5	2.5	4.0	4.2
11 Other unidentified compounds, each <4% dose	5.0	5.5	3.2	5.1
Feces				
Unknown M16	5.7	6.9	0.2	0.1
12 Unidentified compounds, each <4% dose	5.7	6.2	6.3	6.0
Total unidentified [d]	17.9	21.1	20.1	20.3
Total accounted for	87.1	93.6	60.4	75.5
Unaccounted for	12.9	6.4	39.6	24.5
Total	100	100	100	100

a Data were obtained from Tables 7-12 on pages 43-48 of MRID 47090414.

b 14 consecutive daily doses were administered, and results after the final dose are reported as % daily dose.

c Radioactivity was seen as 2 distinct peaks within the region of interest.

d Values of <0.1 were treated as 0 when totaling percentages.

M3 1-(2-fluoro-4,5-(*cis*)-dihydroxy-cyclohexa-2,6-diene)-1-(4-fluorophenyl)-2-(1,2,4triazol-1-yl) ethanol (major)
1-(2-fluorophenyl)-1-(4-flurophenyl-ethan-1,2-diol glucuronide (minor)

M5 1-(2-fluoro-4,5-(*trans*)-dihydroxy-cyclohexa-2,6-diene)-1-(4-flurophenyl)-2-(1,2,4triazol-1-yl) ethanol

M6 1-(2-fluoro-4,5-(*trans*)-dihydroxy-cyclohexa-2,6-diene)-1-(4-flurophenyl)-2-(1,2,4triazol-1-yl) ethanol

M8 1-(2-fluoro-4-hydroxyphenyl)-1-(4-fluorophenyl)-2-(1,2,4triazol-1-yl) ethanol glucuronide and
1-(2-fluoro-4-hydroxy-5-methoxyphenyl)-1-(4-fluorophenyl)-2-(1,2,4triazol-1-yl) ethanol glucuronide

M15 1-(2-fluoro-4-hydroxy-5-methoxyphenyl)-1-(4-fluorophenyl)-2-(1,2,4triazol-1-yl) ethanol NB the order of 4,5 substitution is not confirmed for this compound, AND
1-(2-fluoro-4-hydroxyphenyl)-1-(4-fluorophenyl)-2-(1,2,4triazol-1-yl) ethanol

M18 1-(2-fluorophenyl)-1-(4-fluorophenyl) ethan-1,2-diol

III. DISCUSSION and CONCLUSIONS

A. **INVESTIGATORS CONCLUSIONS:** Flutriafol was extensively absorbed, and excretion was rapid, without pronounced sex differences in excretion profiles. Bile was shown to be an important route of elimination. Slightly more radioactivity was found in the urine than the feces. Retention in tissues was minimal at 7 days post-dose, and whole blood contained the highest amount of radioactivity in the tissues evaluated. Biotransformation was extensive, with only trace amounts of the parent detected in the excreta. The primary site for metabolism was the 2-fluorophenyl ring. Three of the major metabolites were dihydrodiol isomers of flutriafol, and the bulk of the remainder were glucuronide conjugates.

B. **REVIEWER COMMENTS:** More than 78% of the administered dose was recovered in the bile and urine of the single 5 mg/kg (both radiolabels) and 250 mg/kg dose groups. Absorption was generally similar between sexes, radiolabels, and between single and multiple dose regimes. Comparing absorption in 5 mg/kg groups to the 250 mg/kg groups, absorption remains extensive; however, a longer time is required for absorption to complete.

Total recoveries at 168 hours post-dose were 97-99% of the administered single dose and 115-125% daily dose in the multiple dose study. The administered dose was mostly eliminated within 48 hours at 5 mg/kg (86-97% of the single dose or 104% daily dose of the multiple dose groups) and at 250 mg/kg (68-85% dose, except bile duct-cannulated females which was 38% dose).

Only 0.04-0.05% of the dose was present in the expired carbon dioxide in a preliminary study. In the bile duct-cannulation study, most of the radioactivity was excreted in the bile (47-79% of the dose). In the single dose 5 mg/kg group (not bile duct-cannulated), similar amounts of radioactivity were excreted in the feces as in the urine, but only approximately half as much was excreted in the feces as in the urine at 250 mg/kg. Slightly more radioactivity was found in the urine of the multiple dosed animals compared to the single dosed animals. The excretion profile was generally similar between the sexes, and was also similar following 1, 5, 10, and 14 doses.

Tissue distribution was examined in animals sacrificed 168 hours post-dose. In blood, radioactivity partitioned into the red blood cells. In animals receiving multiple doses, concentrations of radioactivity were higher in the blood cells than plasma of males (218-fold) and females (129-fold). Excluding blood cells and GI tract measurements, the highest concentrations were found in whole blood in males (190 ng equivalents flutriafol/g tissue in the single 5 mg/kg dose group, 8040 ng equiv/g in the 250 mg/kg dose group, and 1450 ng equiv/g in the multiple 5 mg/kg/day dose group) and in females (140 ng equivalents flutriafol/g tissue in the single 5 mg/kg dose group, 6740 ng equiv/g in the 250 mg/kg dose group, and 519 ng equiv/g in the multiple 5 mg/kg/day dose group). In both sexes and all groups, concentrations of radioactivity were relatively high in both liver and kidneys. Other organs with high concentrations included the adrenal glands in the single 5 mg/kg females and 250 mg/kg/day females; spleen in the 250 mg/kg males and the multiple 5 mg/kg/day males and females; and pituitary in the multiple 5 mg/kg/day males. Thus, the distribution profiles were generally similar between species, dose level, and single vs multiple dose

regime. A 50-fold increase in dose resulted in an approximately 42-48-fold increase in radioactivity concentrations in the whole blood; thus, the concentrations were roughly proportional to the dose.

The total amount of radioactivity isolated in the tissues and carcass was miniscule: <1% of the administered dose was isolated in the single 5 mg/kg dose groups and 250 mg/kg dose groups and only 3% of the daily administered dose was isolated in the multiple 5 mg/kg dose group. Also, the amount of the dose remaining in the body (GI tract and contents, tissues, and remaining carcass) after 168 hours was <1.1% of the administered dose regardless of sex, radiolabel position, or dose. For these reasons, bioaccumulation in all dose groups was considered unlikely.

GC-MS, LC-MS, LC-MS/MS, and NMR analyses combined with enzyme and acid hydrolysis studies revealed the presence of more than 19 radioactive compounds in the urine and feces and allowed the identification of some of these compounds. Total radiation accounted for in the identified and unidentified components was 87-94% dose at 250 mg/kg and 60-76% at 5 mg/kg (multiple dose); total identified amounted to 69-72% dose at 250 mg/kg and 40-55% dose at 5 mg/kg (multiple dose).

At least thirteen metabolites were isolated but not identified. The parent and the following metabolites were identified:

M3	1-(2-fluoro-4,5-(*cis*)-dihydroxy-cyclohexa-2,6-diene)-1-(4-fluorophenyl)-2-(1,2,4triazol-1-yl) ethanol (major) 1-(2-fluorophenyl)-1-(4-flurophenyl-ethan-1,2-diol glucuronide (minor)
M5	1-(2-fluoro-4,5-(*trans*)-dihydroxy-cyclohexa-2,6-diene)-1-(4-flurophenyl)-2-(1,2,4triazol-1-yl) ethanol
M6	1-(2-fluoro-4,5-(*trans*)-dihydroxy-cyclohexa-2,6-diene)-1-(4-flurophenyl)-2-(1,2,4triazol-1-yl) ethanol
M8	1-(2-fluoro-4-hydroxyphenyl)-1-(4-fluorophenyl)-2-(1,2,4triazol-1-yl) ethanol glucuronide AND 1-(2-fluoro-4-hydroxy-5-methoxyphenyl)-1-(4-fluorophenyl)-2-(1,2,4triazol-1-yl) ethanol glucuronide
M15	1-(2-fluoro-4-hydroxy-5-methoxyphenyl)-1-(4-fluorophenyl)-2-(1,2,4triazol-1-yl) ethanol NB the order of 4,5 substitution is not confirmed for this compound, AND 1-(2-fluoro-4-hydroxyphenyl)-1-(4-fluorophenyl)-2-(1,2,4triazol-1-yl) ethanol
M18	1-(2-fluorophenyl)-1-(4-fluorophenyl) ethan-1,2-diol

Flutriafol is extensively metabolized. The parent was isolated in only trace amounts in the urine and feces (<0.1% of the administered dose, except 0.2-0.4% dose in the feces of the multiple 5 mg/kg dose group). In the single 250 mg/kg dose group, metabolites representing ≥5% of the administered dose included the following: (i) M5, M6, M3, and M15 in the urine of both sexes; (ii) M8 in the urine of females; (iii) M6, M3, and M15 in both sexes in the feces; and (iv) M18 in the feces of males. In the multiple 5 mg/kg dose group, metabolites representing ≥5% of the administered dose included the following: M8, M5, M6, and M3 in the urine of both sexes; and M6 in the feces of females. Unknowns representing more than 5% dose included M9 in the urine of the multiple 5 mg/kg dose males and M16 in the feces of the 250 mg/kg dose males and females. However, reasonable efforts were made to identify all metabolites present at 5% or greater of the administered dose; therefore, the isolation of unknowns at >5% dose was not considered to be a deficiency.

In general, metabolism profiles were similar between sexes. The metabolism profile in urine was similar between the 250 mg/kg dose group and the multiple 5 mg/kg dose group, but the metabolism profiles in feces resulted in the isolation of greater amounts of identified compounds in the high dose group.

Results from MRID 47090413 were not tabulated. Summarizing the Sponsor, the metabolic profiles were similar regardless of the matrix (feces, urine, or bile), the dose, the sex, or the radiolabel. Comparative studies with ^{14}C-carbinol and ^{14}C-triazole labeled flutriafol indicated that only a minor amount of cleavage of the triazole moiety occurred. Urinary metabolites included M15 (11% of administered dose), M8 (8% dose), M5 and M6 (8-10% dose, each), and probably M3 (8% dose). The compound designated as M2C was assigned a structure that differs from M3; however, the structures are similar enough that the compounds could be the same, and M3 is more likely the correct structure.

The primary site for metabolism was the 2-fluorophenyl ring. The initial metabolic step was probably epoxidation followed by either rearrangement to form the dihydrodiol isomers or to form hydroxy or dihydroxy metabolites. The hydroxyl groups on these primary metabolites may then be either conjugated with glucuronic acid or methylated. A second, minor route for metabolism of flutriafol was via the removal of the triazole ring to form 1-(2 fluorophenyl)-1-(4-fluorophenyl)-ethandiol, which is then conjugated with glucuronic acid.

This metabolism study in the rat is classified **acceptable/guideline** and satisfies the guideline requirement for a metabolism study [OPPTS 870.7485, OPP 85-1] in rats.

C. **STUDY DEFICIENCIES:** Tabulated data for the metabolic profiles were not presented in MRID 47090413. As sufficient information was provided in MRID 47090414, the lack of data in MRID 47090413 was considered to be a minor deficiency and does not affect the conclusions of this review. Different rat strains were used during this study which could have resulted in slightly different pharmacokinetic and metabolic profiles. However, sufficient data was generated, and this study was considered acceptable.

ATTACHMENT

The following is Figure 24, page 84 from MRID 47090414

FIGURE 24

Proposed metabolic pathway of flutriafol in the rat